REMARKS/ARGUMENTS

Objection to the Specification

The disclosure has been objected to because the first paragraph does not contain a reference to the parent applications as required. In response to this objection, Applicant has enclosed a copy of the Application Data Sheet (ADS), which was submitted when the instant Application was originally filed. This ADS contains the relevant priority information. 37 CFR 1.76(b)(5) states that providing this information in the Application Data Sheet constitutes the specific reference required by 35 USC 119(e) or 120.

Nonstatutory Double Patenting

Claims 37-46 have been rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-8 of US Patent No. 6,582,945. In response to this rejection, attached is an executed Terminal Disclaimer document prepared under the provisions of 37 CFR 1.321. Applicant notes that MPEP Section 804.02 states specifically that:

> The filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. V. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991). The court indicated that the "filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection".

Rejection Under 35 USC 112, First Paragraph

Claims 37-46 have been rejected under 35 USC 112, first paragraph for lack of enablement. More specifically, the Patent Office states:

> The instant specification teaches that an antibody was made using a statine analog of a transition state that would disaggregate preformed β–amyloid plaques and also had the ability to cross the blood-brain barrier...such an antibody has not been shown that was made using anything other than a statine analog or which has the ability to inhibit the formation of β–amyloid plaques...applicant has not taught one of ordinary skill in the art to make the antibody of the instant claims.

Applicant respectfully traverses this rejection. Applicant's disclosure teaches synthesis of multiple types of transition state analog peptide antigens, including phenylalanine-statine, reduced peptide bond, and phosphoamidate analogs (page 36, line 8 to page 39, line 7; Table 8) in addition to the statine moiety cited by the Patent Office. Applicant's disclosure also teaches synthesis of a series of analogs for each of the statine and phenylalanine-statine transition state antigens (page 36, lines 9 to 27). Applicant's disclosure clearly demonstrates immunization of mice with the phenylalanine-statine, reduced peptide bond, and phosphoamidate analogs as well as the statine antigen (page 39, lines 8-27; Table 8). Monoclonal antibodies to the statine, phenylalanine-statine, and reduced peptide bond analogs were successfully generated (Table 8). Applicant's disclosure also teaches using non-transition-state-analog antigens for the production of antibodies that bind $A\beta_{1-16}$, $A\beta_{14-25}$, $A\beta_{34-43}$, $A\beta_{1-40}$, and $A\beta_{1-43}$ (page 29, lines 4 to 24 and Table 5).

Claim 37 is directed to a bispecific antibody comprising a first antibody binding specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier, and a second antibody specificity which confers the ability of the bispecific antibody to bind to a β–amyloid epitope. As stated in Hayden et al. (*Curr. Opin. Immun.* 9: 201-212 (1997)), "bispecific molecules possess **two unique functions or binding specificities** within a single molecule..." Even though the two domains of a bispecific antibody are contained within a single molecule, it is well understood that the two domains of such a molecule function autonomously, provided that one domain does not interfere with the function of the other. As stated above, Applicant

has exemplified generation of monoclonal antibodies to statine, phenylalanine-statine, and reduced peptide bond analogs as well as to native β-amyloid. One of skill in the art would expect such antibodies, upon incorporation into bispecific antibodies, to retain their unique monoclonal binding specificities.

The production of bispecific antibodies are well known in the art, and as such the production of the same is a matter of routine experimentation. Applicant exemplifies chemically coupling anti-β-amyloid antibodies individually to an antibody binding specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier (page 45, line 1 to page 47, line 6; page 56, line 17 to page 58, line 14). The production of bispecific antibodies using a native β–amyloid epitope or transition state analog other than a statine analog is a matter of routine experimentation based on the teachings of Applicant's disclosure and the knowledge of one of skill in the art. The antibodies of Applicant's disclosure generated from native amyloid, and statine, phenylalanine-statine, and reduced peptide bond analogs can be linked to a second binding specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier using the methods established in the art. Such established techniques include chemical conjugation of two antibody molecules, fusion of two different hybridoma cell lines to create hybrid hybridomas, and genetic manipulation of recombinant molecules (Hayden et al. *Curr. Opin. Immun.* 9: 201-212 (1997)). Bispecific antibodies made in such a manner would be expected to retain the amyloid binding function and cross the blood-brain barrier. One of skill in the art would expect antibodies made using native amyloid, or phenylalanine-statine, reduced peptide bond, or phosphoamidate analogs to be of similar size and charge as that made using a statine analog. Thus, one of skill in the art would not expect the antigen from which the amyloid binding specificity is made to affect its ability to cross the blood-brain barrier when incorporated into a bispecific antibody bearing such function.

Although additional technical features are recited in dependent Claims 38-43, it is respectfully submitted that discussion of these features is not necessary to establish patentability of these claims. Claim 46 is directed to a bispecific antibody wherein the second antibody binding specificity further confers the ability to hydrolytically cleave β-amyloid. Claim 46 has been amended to recite a further limitation that the second antibody specificity stabilizes β-amyloid in a transition state conformation. Once antibodies are generated, as exemplified in Applicant's disclosure, isolating antibodies that hydrolytically cleave β-amyloid is a matter of routine experimentation. First, out of numerous antibodies generated following immunization with transition state analog peptide antigens, including, for example, phenylalanine-statine or reduced peptide bond analogs, a fraction will be directed to an amyloid transition state. A fraction will be directed to the amyloid transition state because transition state analog peptide antigens are to be used as immunogens. This fraction is then assayed for each antibody's ability to bind and catalytically cleave native β-amyloid. A fraction of the antibodies that recognize the transition state will also recognize native β-amyloid because of (1) the similarity in structure of the native peptide to the transition state and (2) the ability of the antibody combining site to force the native peptide into a transition-state-like conformation. Antibodies that are directed to the transition state will ease bound amyloid into a tetrahedral conformation because such a conformation is lower in energy for the complex than the planar state of the native peptide. Once tetrahedral, hydrolysis, and therefore cleavage, occurs unhindered. Applicant stresses that antibodies that recognize the transition state analog and bind to and cleave native amyloid are obtainable because they are **selected for** based on such properties. The selection of the same, as outlined above, is a matter of routine experimentation. Applicant exemplifies experimental selection on pages 40-45 of the specification.

The Patent Office also states:

> The instant specification teaches that an antibody was made using a statine analog of a transition state that would disaggregate preformed β–amyloid plaques...This would appear to be a hydrolytic cleavage of the β –amyloid as in claim 45. However, such an antibody has not been shown that was made using anything other than a statine analog or which has the ability to inhibit the formation of β–amyloid plaques. The process to form the plaques could well involve other processes that are not affected by the antibody. In any case, the specification does not teach that the antibody will do this.

Claims 44 and 45 as amended are directed to bispecific antibodies wherein the second antibody binding specificity further confers the ability to inhibit the formation of amyloid aggregates and plaques and disaggregate performed amyloid aggregates and plaques, respectively. Applicant notes that none of claims 37-45 are specifically directed to hydrolytic cleavage of β–amyloid. In agreement, Applicant's specification states:

> Anti-β–amyloid specific antibodies in the brain can reduce soluble β–amyloid and β-amyloid deposits by three potential mechanisms. An anti-β-amyloid bispecific antibody that tightly binds soluble β-amyloid will not only sequester the peptide but, due to efflux of vectorized molecules from the central nervous system (Kang et al., J. Pharm. Exp. Ther. 269: 344-350 (1994)), may also carry the bound β-amyloid out of the brain, releasing it into the blood stream. Such a clearance mechanism would lead to a continuous cycling of β-amyloid out of the brain... (page 21, lines 11-21).

As stated above, Applicant teaches production of bispecific antibodies from monoclonal antibodies that bind to the full-length β-amyloid peptide (page 30, lines 28-33 and Table 6, page 30). One of skill in the art would expect such antibodies, upon incorporation into bispecific antibodies, to retain their monoclonal binding specificities. Monoclonal antibodies to native β-amyloid have already been shown to have the ability to solubilize β-amyloid aggregates and inhibit the formation of β-amyloid aggregates *in vitro* (Solomon et al., *Proc. Natl. Acad. Sci. USA* 94(8): 4109 (1997); Solomon et al., *Proc. Natl. Acad. Sci. USA* 93(1): 452 (1996)). Catalytic activity aside, the binding of a large >150kDa bispecific antibody molecule to the much smaller 4kDa amyloid peptide would unavoidably greatly alter the chemical activity, and biological

actions of β–amyloid in the brain. Applicant clearly showed that animals treated with an anti-Aβ antibody retained 10-times more labeled $A\beta_{1-40}$ in the circulation, thereby providing evidence that an Aβ antibody can bind to and sequester significant levels of Aβ *in vivo* (page 31, line 19 to page 32, line 2 and Table 7).

Because it is well established that the aggregation of β-amyloid and the deposition of β-amyloid as plaques in the brain are both accelerated by an elevation in the extracellular concentration of β-amyloid (Scheuner et al., *Nature Med.* **2**: 864 (1996); Kowall et al., *Proc. Natl. Acad. Sci.* **88**: 7247 (1991)), one of ordinary skill in the art would readily predict that sequestration of significant levels of β-amyloid would lower the extracellular concentration of amyloid and thereby prevent the formation of β-amyloid aggregates and β-amyloid plaques within the human brain. Any β-amyloid which is sequestered by its interaction with antibodies would be unavailable for aggregate or plaque formation or other harmful effects in the brain. Resulting antibody-dependent processes, which are innate to the immune system and well known to one of skill in the art, would clear and/or destroy the β-amyloid antigen from an individual bearing a bispecific antibody comprising an antibody specificity conferring the antibody the ability to bind to a β–amyloid epitope.

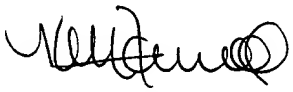
Applicant's disclosure, coupled with the state of the art at the time the instant application was filed, further indicates enablement. A publication printed prior to Applicant's filing date also confirms that Applicant's invention is, in fact, enabling. International Application No. PCT/US98/25386 demonstrates the prophylactic efficacy of the administration of a β-amyloid peptide in treating Alzheimer's disease (page 32, line 36 to page 33, line 12). Immunizations with a β-amyloid peptide were shown to be effective in reducing the amyloid burden in mice and preventing further amyloid deposition over time relative to a control (page 41, line 13 to page 42, line 8). One of skill in the art would predict with a high degree of certainty, based on the

teachings of Applicant's disclosure and the knowledge of one of skill in the art at the time of Applicant's filing, that a bispecific antibody comprising an antibody specificity conferring the ability of the bispecific antibody to bind to a β-amyloid epitope would be effective in sequestering and/or cleaving endogenous β-amyloid in the human, thereby inhibiting the formation of both β-amyloid aggregates and plaques in the brain of the human.

Summary

In light of the above amendment, consideration of the subject patent application is respectfully requested. Any deficiency or overpayment should be charged or credited to Deposit Account No. 500282.

Respectfully submitted,



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